

WHAT IS CLAIMED IS:

1. A controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof for oral administration.

2. A controlled release preparation as claimed in Claim 1 containing from about 50 to about 800 mg of tramadol (calculated as tramadol hydrochloride).

3. A controlled release preparation as claimed in Claim 1, having an in-vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37°C and using UV detection at 270 nm) as set forth below:

<u>TIME (H)</u>	<u>% RELEASED</u>
1	0-50
2	0-75
4	3-95
8	10-100
12	20-100
16	30-100
24	50-100
36	>80

4. A controlled release preparation as claimed in Claim 1, having an in-vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37°C and using UV detection at 270 mm) as set forth below:

<u>TIME (H)</u>	<u>% RELEASED</u>
1	20-50
2	40-75
4	60-95
8	80-100
12	90-100

5. A controlled release preparation as claimed in Claim 1, having an in-vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37°C and using UV detection at 270 mm) as set forth below:

<u>TIME (H)</u>	<u>% RELEASED</u>
1	0-50
2	0-75
4	10-95
8	35-100
12	55-100
16	70-100
24	>90

6. A controlled release preparation as claimed in Claim 1, having an in-vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37°C and using UV detection at 270 mm) as set forth below:

<u>TIME (H)</u>	<u>% RELEASED</u>
1	0-30
2	0-40
4	3-55
8	10-65
12	20-75
16	30-88
24	50-100
36	>80

7. A controlled release oral dosage form according to claim 1, comprising a therapeutically effective amount of tramadol or a salt thereof in a matrix adapted to provide a controlled release of the tramadol or salt thereof upon oral administration.

8. A dosage form according to claim 7, wherein said matrix comprises a controlled release matrix comprising at least one alkylcellulose, at least one C<sub>12</sub> to C<sub>36</sub>, aliphatic alcohol and, optionally at least one polyalkylglycol.

9. A dosage form as claimed in claim 8, wherein said optionally at least one polyalkylglycol is polyethylene glycol.

10. A dosage form according to claim 8, wherein said at least one  $C_{12}$  to  $C_{36}$  aliphatic alcohol is a  $C_{14}$  to  $C_{22}$  aliphatic alcohol.

11. A dosage form according to claim 8, wherein said alkylcellulose is a  $C_1$ - $C_6$  alkylcellulose.

12. A dosage form according to claim 8, characterized in that the dosage form contains from about 1 to about 20% w/w, preferably from about 2 to about 15% w/w of one or more alkylcelluloses.

13. A dosage form according to claim 8, wherein said aliphatic alcohol is selected from the group consisting of lauryl alcohol, myristyl alcohol, stearylalcohol, cetyl alcohol, cetostearyl alcohol, and mixtures of any of the foregoing.

14. The dosage form of claim 13, wherein said aliphatic alcohol is cetyl alcohol or cetostearyl alcohol.

15. A dosage form according to claim 8, wherein said dosage form contains from about 5 to about 30% w/w of aliphatic alcohol.

16. A dosage form according to claim 8, wherein said dosage form contains from about 10 to about 25% w/w of aliphatic alcohol.

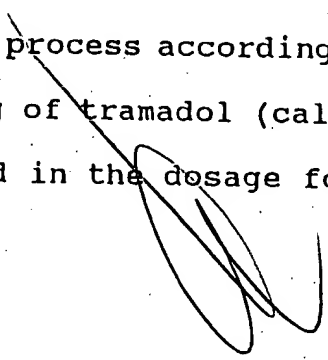
17. A dosage form according to claim 1, in the form of film coated spheroids, wherein said spheroid matrix comprises a spheronizing agent, preferably microcrystalline cellulose.

18. A dosage form according to claim 1, in the form of multi-particulates wherein said matrix comprises a hydrophobic fusible carrier or diluent having a melting point from 35 to 140°C and optionally a release control component comprising a water soluble fusible material, or a particulate soluble or insoluble organic or inorganic material.

19. A dosage form according to claims 1, which comprises a tablet formed by compressing a multiparticulate according to Claim 18.

20. A process for the preparation of a solid, controlled release oral dosage form, comprising incorporating a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof in a matrix adapted to provide a controlled release of the tramadol or salt thereof upon oral administration.

21. A process according to claim 20, wherein from about 50 to about 800 mg of tramadol (calculated as tramadol hydrochloride) is incorporated in the dosage form.



22. A process according to claim 20, wherein the dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37°C and using UV detection at 270 nm) is as set forth below:

<u>TIME (H)</u>	<u>% RELEASED</u>
1	0-50
2	0-75
4	3-95
8	10-100
12	20-100
16	30-100
24	50-100
36	>80

23. A process according to claim 20, wherein the dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37°C and using UV detection at 270 nm) is as set forth below:

<u>TIME (H)</u>	<u>% RELEASED</u>
1	0-50
2	0-75
4	10-95
8	35-100
12	55-100
16	70-100
24	>90

24. A process according to claim 20, wherein the dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37°C and using UV detection at 270 nm) is as set forth below:

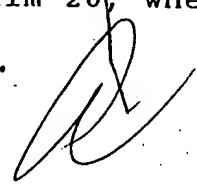
<u>TIME (H)</u>	<u>% RELEASED</u>
1	0-50
2	0-40
4	3-55
8	10-65
12	20-75
16	30-88
24	50-100
36	>80

25. A process according to claim 20, wherein said matrix comprises a controlled release matrix comprising at least one C<sub>1</sub> to C<sub>6</sub> alkylcellulose, at least one C<sub>12</sub> to C<sub>36</sub> aliphatic alcohol and, optionally at least one polyalkylglycol.

26. A process according to claim 25, wherein said aliphatic alcohol is a C<sub>14</sub> to C<sub>22</sub> aliphatic alcohol.

27. A process according to claim 25 wherein said optionally at least one polyalkylglycol is polyethylene glycol.

28. A process according to claim 20, wherein said at least one alkylcellulose is ethylcellulose.



29. A process according to claim 20, wherein said dosage form comprises from about 1 to about 20% w/w of one or more alkylcelluloses.

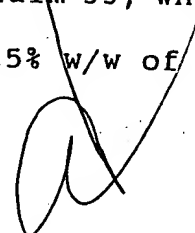
30. A process according to claim 29, wherein said dosage form contains from about 2 to about 15% w/w of one or more alkylcelluloses.

31. A process according to claim 20, wherein said aliphatic alcohol comprises lauryl alcohol, myristyl alcohol or stearyl-alcohol.

32. A process according to claim 31, wherein said aliphatic alcohol is cetyl alcohol or cetostearyl alcohol.

33. A process according to claim 20, wherein said dosage form comprises from about 5 to about 30% w/w of aliphatic alcohol.

34. A process according to claim 33, wherein said dosage form comprises from about 10 to about 25% w/w of aliphatic alcohol.





35. A process according to claim 20, further comprising:

- (a) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof and one or more alkylcelluloses,
- (b) mixing the alkylcellulose containing granules with one or more  $C_{12-36}$  aliphatic alcohols; and, optionally
- (c) shaping and compressing the granules, and film coating, if desired.

36. A process according to claim 20, further comprising:

- (a) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof, lactose and one or more alkylcelluloses with one or more  $C_{12-36}$  aliphatic alcohol; and, optionally,
- (b) shaping and compressing the granules, and film coating.

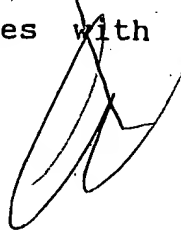
37. A process according to claim 20, further comprising:

- (a) granulating the mixture comprising tramadol or a pharmaceutically acceptable salt thereof and a spheronizing agent;
- (b) extruding the granulated mixture to give an extrudate;
- (c) spheronizing the extrudate until spheroids are formed; and
- (d) coating the spheroids with a film coat.

38. A process according to claim 20, comprising:

- (a) mechanically working in a high-speed mixer, a mixture of tramadol or a pharmaceutically acceptable salt thereof in particulate form and a particulate, hydrophobic fusible carrier or diluent having a melting point from 35 to 140°C and optionally a release control component comprising a water soluble fusible material, or a particulate soluble or insoluble organic or inorganic material at a speed and energy input which allows the carrier or diluent to melt or soften, whereby it forms agglomerates;
- (b) breaking down the larger agglomerates to give controlled release seeds;
- (c) continuing mechanically working with optionally a further addition of low percentage of the carrier or diluent; and
- (d) optionally repeating steps (c) and possibly (b) one or more times.

39. A process according to claim 20, characterized by forming a drug mixture of dry active ingredient and fusible release control materials followed by mechanically working the mixture in a high speed mixer with an energy input sufficient to melt or soften the fusible material whereby it forms particles with the active ingredient.



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41. A process according to claim 20, comprising compressing particles obtained by the process of claim 39.

Year	1954	1955	1956	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100
1954	1955	1956	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	